16 Chronic myeloid leukemia

Kendra L. Sweet and Ehab L. Atallah

Overview, incidence, and prevalence 454
Pathobiology 454
Diagnosis 456
Chronic-phase CML 457
Accelerated-phase CML 465
Blast-phase CML 466
Additional treatment strategies 470
Stem cell transplantation 470
Parenting children 471
Bibliography 472

The online version of this chapter contains an educational multimedia component on practical considerations for monitoring the response to TKIs in CML.

Conflict-of-interest disclosure: Kendra L. Sweet: research funding: Incyte; honorarium: Astellas; membership on advisory boards: Novartis, Bristol Myers Squibb, Arog. Ehab L. Atallah: consultancy: Pfizer, Celgene, Novartis, Takeda; research funding: Novartis, Takeda.

Off-label drug use: Not applicable.

Overview, incidence, and prevalence

Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm characterized by the *BCR-ABL1* fusion gene, which is usually derived from a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11), resulting in a derivative chromosome known as the Philadelphia (Ph) chromosome. CML accounts for 15% to 20% of adult leukemia cases. The worldwide annual incidence of CML is one to two cases per 100,000 persons, with a slight male predominance (male-to-female ratio, 1.3:1). Because successful targeted therapy has returned life expectancy to that of the unaffected general population in many, the prevalence of CML continues to increase and is projected to reach 150,000 cases in the United States by 2040. In Europe, the median age of diagnosis ranges between 60 and 65 years, and in the United States, CML is most frequently diagnosed in individuals between the ages of 65 and 74. However, in countries where life span is shorter, the median age of diagnosis is substantially lower. CML in children and young adults is rare, constituting only 2% of all leukemias in children <15 years of age and 9% of all leukemias in adolescents 15 to 19 years of age. Radiation exposure has been implicated as a risk factor; however, unlike other myeloid leukemias, there has been no evidence for a causal association between CML and exposure to organic solvents, industrial chemicals, or alkylating agents.

Pathobiology

The Philadelphia chromosome was initially identified in 1960. As shown in Figure 16-1, the t(9;22)(q34;q11) translocation in CML juxtaposes the 3′ segment of the *c-ABL* oncogene (normally encoding the Abelson tyrosine kinase [TK]) from the long arm of chromosome 9 to the 5′ part of the breakpoint cluster region (*BCR*) gene on the long arm of chromosome 22. The resultant hybrid oncogene is transcribed as a chimeric *BCR-ABL1* mRNA, which, in turn, is translated into a functional abnormal protein. At diagnosis, the characteristic t(9;22)(q34;q11) is present in approximately 95% of CML cases. The remaining cases have either variant translocations involving a third and sometimes a fourth chromosome or cryptic translocations. In these cases, routine cytogenetic analysis may be unable to detect the Ph chromosome, and the diagnosis relies on demonstration of either gene fusion by interphase fluorescence in situ

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

CLINICAL CASE

A 64-year-old male computer engineer with a history of coronary artery disease and type 2 diabetes was seen by his primary care physician because of progressive fatigue, left upper quadrant abdominal discomfort, unintentional weight loss, and drenching night sweats of 2 months' duration. Physical examination was remarkable for palpable splenomegaly measuring 6 cm below the left subcostal margin. Routine complete blood count showed leukocytosis (white blood cells [WBCs] = 87×10^9/L) with predominance of neutrophils and neutrophil precursors (10% myelocytes, 5% metamyelocytes), normocytic anemia (hemoglobin = 10.2 g/dL, hematocrit = 35%, mean corpuscular hemoglobin = 85 fL), and an elevated platelet count (platelets = 486×10^9/L). Also noted on laboratory examination were basophilia (4%), eosinophilia (3%), and blasts (1%). A bone marrow aspirate and biopsy were performed and showed a hypercellular marrow (100% cellularity) with granulocytic proliferation. Metaphase cytogenetics showed t(9;22)(q34;q11) [20] in all cells, but no other additional cytogenetic aberrations were detected. Reverse transcriptase–quantitative polymerase chain reaction (RT-qPCR) for *BCR-ABL1* mRNA transcripts on the International Scale (IS) in the peripheral blood was 84%. The Sokal risk score was calculated at 0.82 (intermediate risk).

hybridization (FISH) or the fusion transcript by reverse transcriptase–polymerase chain reaction (RT-PCR).

Three separate breakpoint regions in the *BCR* gene are associated with distinct disease phenotypes. In typical CML, the *BCR* gene interruption occurs in a region referred to as the major breakpoint cluster region (*M-BCR*). *M-BCR* joins with sequences from *c-ABL* and forms the *BCR-ABL1* fusion. The *BCR-ABL1* transcripts are translated into 210-kDa proteins, collectively known as p210 BCR-ABL1. There are two main variants: e13a2 and e14a2.

Less frequently, a downstream locus of *BCR* (*mu-BCR*) joins the same *c-ABL* sequence forming a 230-kDa protein, known as p230 BCR-ABL1. Clinically, these cases present with neutrophilia, with or without thrombocytosis, and often have a more indolent clinical course than those with p210 BCR-ABL1. Finally, the minor *BCR* breakpoint region (*m-BCR*) juxtaposes the same *c-ABL* resulting in smaller 190-kDa p190 BCR-ABL1 protein product. This is most often found in de novo acute lymphoblastic leukemia (ALL), although it can be detected in CML as well, either coexpressed with p210 BCR-ABL1 (5%–10% of cases) or detected alone in atypical cases that are often associated with monocytosis. BCR-ABL interacts with several signaling pathways which lead to leukemogenesis. These include the RAS pathway, JAK-STAT

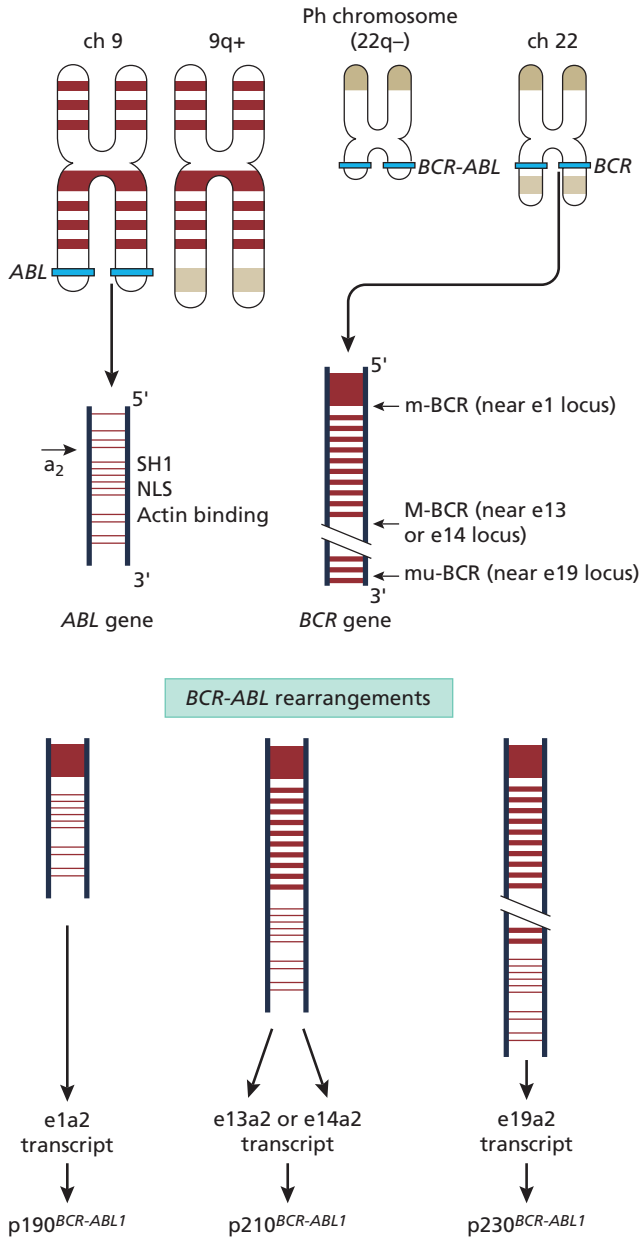

Figure 16-1 Molecular pathogenesis of t(9;22)(q34;q11) in CML. The 3′ portion of the *ABL* gene on the telomeric region of the long arm of chromosome 9 is translocated to the *BCR* gene on chromosome 22 to form the characteristic 22q− abnormality referred to as the Philadelphia (Ph) chromosome. Breakpoints in the ABL gene can occur, upstream of exon Ib, between exons Ib and Ia, or downstream of exon Ia. The a2 and downstream exons of ABL encode the Src homology (SH) domains of the ABL kinase, including the SH1/tyrosine kinase domain, DNA binding domain, nuclear localization signal (NLS), and actin binding site. The breakpoints on chromosome 22 occur at one of three locations in *BCR*, yielding hybrid oncogenes of varying length consisting of 5′ *BCR* sequences and 3′ *ABL* sequences. Each hybrid oncogene gives rise to a chimeric transcript, which encodes a fusion protein with oncogenic activity. These include $p190^{BCR\text{-}ABL1}$ (resulting from fusion at the minor breakpoint or m-BCR site), the $p210^{BCR\text{-}ABL1}$ gene product (resulting from fusion at the major breakpoint or M-BCR site), and $p230^{BCR\text{-}ABL1}$ (resulting from fusion at the micro breakpoint or mu-BCR site).

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

pathway, phosphatidylinositol-3 (PI3) kinase pathway, and many others such as SYP, FES, and CBL.

At the molecular level, mutations in the kinase domain of *BCR-ABL1* can emerge. Resistance to tyrosine kinase inhibitor (TKI) therapy is often characterized as primary or secondary (ie, acquired) resistance. The etiology of primary resistance remains largely unknown, but reported mechanisms include altered drug transport and BCR-ABL–independent mechanisms (where BCR-ABL remains inhibited, but disease is not significantly altered or disease progression occurs). Although point mutations in the ABL tyrosine kinase domain (TKD) are rarer in primary resistance, they are a common cause of acquired TKI resistance and the incidence of mutations increases in advanced disease. Approximately 25% of patients in chronic phase (CP) who develop resistance to imatinib have an ABL TKD mutation. Importantly, identification of a TKD mutation can influence treatment selection after an inadequate response and/or TKI resistance is encountered. Mutations are currently detected using technology involving Sanger sequencing, where the clone affected by the mutation forms at least 20% of the residual leukemia. More than 80 point mutations have been described after imatinib exposure, but substitutions at seven amino acid residues (G250, Y253, E255, T315, M351, F359, and H396) comprise ~60% of mutations reported in larger surveys. Subsequent TKI generations have been designed to minimize resistance due to mutations. Dasatinib resistance–associated mutations include T315I, F317L/V/I/C, and V299L. The Y253H, E255K/V, T315I, and F359V/C/I mutations are associated with nilotinib resistance, and L248V, G250E, V299L, T315I, and F359C are associated with bosutinib resistance (Table 16-1). Ponatinib treats CML with any mutation, including T315I; rare compound mutations (ie, mutations on the same DNA strand) have been described but may not contribute significantly to ponatinib resistance. The importance of lower-level mutations identified by newer methodologies of next-generation sequencing is currently under investigation by a number of groups.

Table 16-1 Recommendations for selecting next-line therapy after TKD mutation detection

Mutation	Treatment recommendation
Y253H, E255K/V, F359V/C/I, or G250E*	Dasatinib
F317L/V/I/C, T315A, V299L, or G250E*	Nilotinib
E255K/V, F317L†/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Asciminib,‡ ponatinib, omacetaxine, allogeneic SCT, or clinical trial

The most common mutations detected are shown. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.3.2022. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

*G250E is listed as a contraindicated mutation to bosutinib in the NCCN Guidelines V3.2022. Dasatinib could be a treatment option for patients with G250E.

†Bosutinib has minimal activity against the F317L mutation. Nilotinib may be preferred over bosutinib for patients with an F317L mutation.

‡Asciminib is a treatment option for CP-CML patients with the T315I mutation.

Diagnosis

The majority of CML patients present with CP disease, most commonly with an insidious onset, and are diagnosed based on abnormalities observed on complete blood count. Common symptoms at presentation can include fatigue, night sweats, weight loss, and gout attacks. Many patients also present with splenomegaly (50%-90%) at diagnosis, which may be symptomatic. Thrombotic and hemorrhagic complications are relatively infrequent (<5%), although purpura is a common complaint. Hyperleukocytosis alone does not routinely cause symptoms because of the relative maturity of the leukemic cells and their smaller size compared with the immature, large, poorly deformable blast cells seen in acute leukemia; however, in rare cases, patients can present with visual disturbances, including retinal hemorrhage, and males with very high WBC counts can present with leukostasis-related priapism. A progressively severe symptom burden, marked by constitutional symptoms, including fever, night sweats, weight loss, bleeding, bone pain, and worsening splenomegaly, may herald onset of accelerated-phase (AP) or blast-phase (BP) CML, defined in the following.

A suspected case of CML can be confirmed by assays of the peripheral blood to detect either the *BCR-ABL1* fusion gene at the chromosome level or its chimeric transcripts. At diagnosis, the sensitivity of FISH or RT-PCR of peripheral blood is equal to that of bone marrow. FISH allows for identification and quantitation of the chimeric oncogene among interphase nuclei on a peripheral blood smear; usually, 200 to 500 nuclei are screened. RT-PCR is carried out on peripheral blood–derived RNA and is an extremely sensitive technique; RT-PCR can detect the *BCR-ABL1* transcript in <1 of 10^5 cells in most laboratories. The sensitivity of a given qRT-PCR test depends on both the quality of the test and sample. As such, the maximum depth of response that can be reported is limited by the dynamic range reached. The term "complete molecular response" should be avoided, as it reflects different depths of response in different samples, but no absolute value.

Both methods can detect "masked" or cryptic chromosomal translocations that are missed by conventional

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

cytogenetics in ~5% of cases. FISH has the advantage of identifying unusual variant rearrangements that are outside the regions amplified by the RT-PCR primers. The RT-PCR method, unlike FISH, can differentiate between the fusion genes encoding the p190, p210, and p230 BCR-ABL1 products. Additionally, RT-PCR provides more accurate detection and quantification when disease levels are low. Because of the lower cost, ability to discriminate breakpoints, and accurate quantitation at low levels of disease burden, RT-PCR is the preferred assay for CML diagnosis and monitoring.

In the peripheral blood, neutrophilia and immature circulating myeloid cells, with an increase in myelocytes, are hallmark features of CP CML. More than 50% of patients present with a WBC count of >100 × 10^9/L, with blasts usually accounting for <2% of the WBCs. Absolute basophilia is usually present, and eosinophilia is common. Anemia may be present in up to one half of patients. Roughly 15% to 35% of patients present with platelet counts of >700 × 10^9/L, although extreme thrombocytosis (ie, >1500 × 10^9/L) is uncommon. The high cell turnover and hypercatabolic state of CML are associated with elevated lactate dehydrogenase and uric acid levels.

Although a positive RT-PCR or FISH assay in the peripheral blood confirms the diagnosis of CML, some but not all experts recommend a bone marrow evaluation at the time of diagnosis. A marrow sample at diagnosis will provide an assessment of the percentage of blasts and identify additional chromosomal abnormalities (ACAs), which impact prognosis and allows for correct staging of the disease. The marrow in CP CML typically shows myeloid hyperplasia and an elevated myeloid-to-erythroid ratio (often >10:1). Bone marrow blasts are <10%. Maturation of precursors is normal in CML, and dysplastic features are not routinely found. Megakaryocytes are often smaller than normal in contrast to large megakaryocytes, which can be seen in other myeloproliferative neoplasms, and show hypolobation, clustering, and peritrabecular localization. Marrow basophilia is noted in one-fourth of cases. A progressive symptom burden and change in laboratory and bone marrow characteristics mark progression to AP or BP CML; these abnormalities are summarized in Table 16-2.

Chronic-phase CML

Prognosis

Historically, patients diagnosed with CP CML remained stable for an average of 3 to 5 years before progressing to AP or BP CML. Before the development of TKIs, patients with CML who did not undergo stem cell transplantation (SCT) had a median survival of roughly 5 to 7 years, and 30% of patients survived beyond 10 years. In 2001, the first BCR-ABL TKI, imatinib, gained regulatory approval.

Table 16-2 Pathologic features of accelerated- and blast-phase CML

	WHO	CIBMTR	ELN	MDACC
Accelerated phase	Increasing WBC count unresponsive to therapy Peripheral blood basophils ≥20% Persistent thrombocytopenia (<100 × 10^9/L) unresponsive to therapy Blasts 10%-19% in the peripheral blood and/or nucleated bone marrow cells Cytogenetic evidence of clonal evolution	10%-19% blasts in blood or marrow ≥20% basophils in peripheral blood, Clonal marrow cytogenetic abnormalities, in addition to the single Philadelphia chromosome (clonal evolution) Increasing spleen size, unresponsive to therapy Increasing WBC, unresponsive to therapy Thrombocytopenia (platelets <100,000), unrelated to therapy Thrombocytosis (platelets >1,000,000), unresponsive to therapy	Blasts in blood or marrow 15%-29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% Basophils in blood ≥20% Persistent thrombocytopenia (<100 × 109/L) unrelated to therapy Clonal chromosome abnormalities in Ph^+ cells (CCA/Ph^+), major route, on treatment	Peripheral blood blasts ≥15% and <30% Peripheral blood blasts and promyelocytes combined ≥30% Peripheral blood basophils ≥20% Platelet count ≤100 × 10^9/L unrelated to therapy Additional clonal cytogenetic abnormalities in Ph^+ cells
Blast phase	Blasts ≥20% of peripheral blood white cells or of nucleated bone marrow cells Extramedullary blast proliferation Large foci or clusters of blasts in the bone marrow biopsy	≥20% blasts (formerly ≥30%) in the peripheral blood or bone marrow Extramedullary blastic infiltrates	Blasts in blood or marrow ≥30% Extramedullary blast proliferation, apart from spleen	≥30% blasts in PB or bone marrow Extramedullary blast proliferation

PB, peripheral blood.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

This has dramatically altered the natural history of CML, resulting in marked improvements in survival. Before the development of TKIs, multivariate prognostic models (eg, the 1984 Sokal score, including age, spleen size, platelet counts, and percent blasts) and the 1998 Hasford (Euro) score (added eosinophil and basophil percentage to Sokal score) were useful to help define the overall survival of patients with CML. Colleagues from the European LeukemiaNet (ELN) have attempted to improve upon these scores using large cohorts of patients treated with TKI from diagnosis. The European Treatment and Outcome Study for CML (EUTOS) score was developed to predict complete cytogenetic response (CCyR) at 18 months and has not proved to be a consistent predictor of overall survival (OS) or progression free survival (PFS). This may reflect the fact that CML per se is now a rare cause of death and patients are more likely to succumb to other medical conditions. The EUTOS long-term survival score has recently been developed to try to predict death from disease. Although these scoring systems are useful, particularly in the context of choosing first-line therapy, the most important prognostic indicators remain phase of disease at diagnosis and the speed and depth of response to TKI therapy. Notably, prognostic risk scores have not been validated in children and may not apply.

Molecular monitoring and milestones on TKI therapy

The development of TKIs has completely changed the standard therapeutic approach for all phases of CML, and response to these therapies has a substantial impact on prognosis. As such, response to therapy and many clinical trial end points are measured by meeting certain treatment responses or "milestones" at particular times in the treatment course. Criteria for complete hematological response (CHR) include resolution of symptoms and signs of the disease, including palpable splenomegaly, leukocytes $<10 \times 10^9$/L and absence of immaturity (myelocytes, promyelocytes, blasts, etc), and platelets $<450 \times 10^9$/L. Complete cytogenetic response (CCyR) is achieved if there are no Ph-positive metaphases, whereas partial cytogenetic response (PCyR) is characterized by 1% to 35% Ph-positive metaphases, major cytogenetic response (MCyR) by 0% to 35% Ph-positive metaphases (complete plus partial), and minor responses by >35% Ph-positive metaphases. Molecular responses are reported as a percentage of the ratio of *BCR-ABL1* transcripts to those of a control gene. Two common control genes are *ABL1* and *BCR*. Peripheral blood is the preferred source, not only due to ease of sampling, but also because it has been shown to correlate with results from bone marrow samples and because the majority of clinical trial data have been reported from peripheral blood measurements. The International Scale was developed to harmonize molecular responses (MRs) across laboratories. IS response is derived by applying a laboratory-specific conversion factor to molecular response data from each individual participating laboratory. This conversion factor is derived from comparison to a reference laboratory and is monitored over time for "drift" in IS measurements. All molecular response criteria and recommendations for intervention in the National Comprehensive Cancer Network (NCCN) or ELN guidelines are based upon IS molecular response. It is important to note that the ability to report specific depths of response is dependent on the quality of the control mRNA values.

The NCCN and ELN recommendations specify molecular monitoring at 3-month intervals and are generally based upon observations regarding outcomes from clinical trials. A major molecular response (MMR) is defined as *BCR-ABL1* IS transcripts of 0.1% or less. Deep molecular responses include MR4 (*BCR-ABL1* ≤0.01%) and MR4.5 (*BCR-ABL1* ≤0.0032%). Definitions of response are shown in Table 16-3. Early molecular response (EMR; *BCR-ABL1* transcripts ≤10%) at 3 months is associated with good prognosis, and treatment guidelines recommend that *BCR-ABL1* transcripts >10% be considered a warning and are a trigger to examine patient adherence and assess for resistance. A study of 1440 patients treated on the German CML Study IV observed that among the 28% of patients who did not achieve ≤10% *BCR-ABL1*, OS after 5 years was poorer at 87% versus 94% for patients >1% but ≤10% and as compared to 97% for patients ≤1%. Other studies have confirmed that early response at 3 months is associated with response, PFS, and OS in patients treated with second-generation TKIs. The benefit in improved PFS and OS for patients who achieve EMR is similar across studies and is ~10% to 15%. Although fewer patients achieve EMR on imatinib at 400 mg daily, the impact of achieving EMR on outcomes is similar for first- and second-generation TKIs. Not achieving EMR is likely a marker of poor biology, as more patients with high-risk Sokal scores do not achieve EMR. However, it may also reflect poor adherence. Although, the improved prognosis associated with EMR at 3 months is unquestioned, current treatment recommendations identify *BCR-ABL1* transcripts >10% as a warning rather than failure and suggest that response at 6 months can influence decisions to alter therapy. This recommendation is based not only upon observations from several studies, but also on a lack of evidence that very early change alters outcome. A study of 320 imatinib-treated patients demonstrated that patients with *BCR-ABL1* transcripts >10% at

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Table 16-3 Definitions of response

Response	Definition
CHR (complete hematologic response)	Leukocyte count <10 × 10^9/L; platelet count <450 × 10^9/L; normal differential with no early forms; no splenomegaly
MCyR (major cytogenetic response)	0%-35% Ph-positive metaphases (marrow)
PCyR (partial cytogenetic response)	1%-35% Ph-positive metaphases (marrow)
CCyR (complete cytogenetic response)	0% Ph-positive metaphases (marrow)
MMR (major molecular response)	*BCR-ABL1* IS ≤0.1%
MR (deep molecular response)	*BCR-ABL1* IS ≤0.01% (MR4)
	BCR-ABL1 IS ≤0.0032% (MR4.5)
	Undetectable *BCR-ABL1* (assay sensitivity ≥4.5 logs)

Common control genes are *ABL1* and *BCR*.

BCR-ABL1 IS, percentage *BCR-ABL1*/control gene, standardized to the International Scale.

3 months but <1% at 6 months had no significant difference in PFS as compared to patients achieving *BCR-ABL1* transcripts <10% at 3 months. The Australian group reported similar observations among 528 imatinib-treated patients and identified that only the group of patients with *BCR-ABL1* transcripts >10% at 6 months had poorer PFS and OS. Similar observations at 6 months have been made for patients treated with frontline nilotinib and dasatinib. It is not clear how early treatment interruptions to manage side effects have influenced these analyses, such that the 3-month milestone might be too early to definitively assess efficacy. Additional milestones are based upon molecular and cytogenetic data demonstrating the association between PFS, event free survival (EFS), and OS and response at particular time points during therapy.

After 12 months on TKI therapy, the optimal molecular response is MMR, particularly in patients who have a long-term goal of treatment-free remission (TFR). However, in patients whose goal is long-term survival without an attempt at TFR, a molecular response <1% is considered sufficient to achieve this goal. *BCR-ABL1* transcripts of <1% are roughly equivalent to CCyR, and most physicians now use molecular testing rather than the more invasive bone marrow karyotyping. For the IRIS trial at 6-year follow-up, the EFS rate was 59%, 85%, and 91% for patients with no cytogenetic response, MCyR, or CCyR at 6 months, respectively, and other studies have demonstrated improved OS in patients with CCyR at 6 or 12 months. MMR is associated with improved EFS and PFS and decreases the risk for loss of response, but the time at which MMR should be achieved is more controversial. Although achievement of a deep molecular response does not equate to improved OS, the opportunity to attempt TKI cessation cannot be offered to patients who have not achieved deep molecular responses. Optimal response milestones have been clearly established by the NCCN (Figure 16-2) and the ELN (Table 16-4).

Selecting first-line TKI therapy in CP CML

Currently, 5 BCR-ABL1 TKIs have been given regulatory approval for treatment of CML and four have an indication for first-line use. All are excellent choices, and there is no "right way" to select therapy. Overall, the goals of care are (1) to ensure response milestones are met, as this will ensure normal life span; (2) to optimize quality of life while the patient is taking daily medication; (3) to minimize longer-term potentially irreversible toxicities; and (4) to achieve durable, deep molecular responses such that a trial of TKI cessation may be considered. First and foremost, the initial goal of ensuring response milestones are met in order to prevent progression to advanced phases of CML is the most important. Longer follow-up of second-generation TKIs has not found statistically significant differences in OS or PFS for these drugs as compared to imatinib when used first-line. Nonetheless, there are benefits from the use of first-line second-generation TKIs as compared to imatinib. These benefits include the development of fewer mutations conferring TKI resistance, decreased rates of progression to AP and BP, and more rapid achievement of MMR or MR4.5 (Table 16-5). Even so, there are unique, and potentially life-altering, side effects associated with second-generation TKIs that must be considered. These include the increased risk for cerebrovascular, cardiovascular, and peripheral arterial events with nilotinib and pleural effusions and pulmonary hypertension with dasatinib. Consequently, a patient's medical history and family history, together with their personal therapy goals, should be used to guide selection of first-line, second-generation TKIs. For example, avoiding nilotinib

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

BCR-ABL1 (IS)	3 months	6 months	12 months
>10%	Yellow	Red	
>1% – 10%	Green		Yellow
>0.1% –1%	Green		Light green
≤0.1%	Green		

Color	Concern	Clinical considerations	Recommendations
Red	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
Yellow	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI (CML-5) or continue same TKI (other than imatinib) (CML-5) or increase imatinib dose to a maximum of 800 mg and consider evaluation for allogeneic HCT
Light Green	TKI-sensitive disease	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient
Green	TKI-sensitive disease	• Monitor response (CML-E) and side effects	Continue same TKI (CML-G)

Figure 16-2 Expected milestones and response to first-line TKI therapy as recommended by NCCN. Redrawn and adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.3.2022. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

in patients with cardiovascular disease, diabetes mellitus, and/or uncontrolled hyperlipidemia is preferred. Avoiding dasatinib in patients with congestive heart failure or a history of pleural effusion and avoiding bosutinib in patients prone to diarrhea (eg, inflammatory bowel disease) are also reasonable strategies. Imatinib not only remains the most cost-effective choice, but also is the TKI with the longest safety track record. Imatinib is an excellent choice for many patients, including older patients with medical comorbidities. Scenarios in which to consider second-generation TKI in the first-line treatment of patients with CP CML include a high-risk Sokal score, and patients with additional chromosomal abnormalities at diagnosis. There is also an argument to consider second-generation TKI in younger female patients who may want to achieve deep responses quickly in order to plan treatment interruption for the purposes of family planning. Finally, approximately a third of patients end up switching off the initial TKI. Most common reasons for discontinuation are intolerance or resistance.

Table 16-4 Expected milestones and response to first-line TKI therapy expressed as BCR-ABL1 on the International Scale (IS) (EMSO provisional adaptation of ELN 2020 recommendations)

Time	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 mo	≤10%	>10%	>10% if confirmed within 1-3 mo
6 mo	<1%	>1%-10%	>10%
12 mo	≤0.1%	>0.1%-1%)	>1%
Any time	≤0.1%	>0.1%-1%, loss of ≤0.1% (MMR)*	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR4).

A change of treatment may be considered if MMR is not reached by 36-48 months.

ACA, additional chromosomal abnormalities in Ph^+ cells; ELTS, EUTOS long-term survival score; NA, not applicable.

*Loss of MMR (BCR-ABL1 >0.1%) indicates failure after TFR.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Table 16-5 Largest randomized trials comparing frontline imatinib with second-generation TKIs

Clinical trial	TKI vs imatinib (I) 400 mg daily	CCyR by 12 months	MR3 by 12 months	MR3 by 5 years	MR4 by 5 years	MR4.5 by 5 years	Progression to AP/BP	OS at 5 yrs
DASISION (*N* = 519)	Dasatinib 100 mg daily	77	46	76	NR	42	5	91
	Imatinib 400 mg daily	67	28	64	NR	33	7	90
ENESTnd (*N* = 846)	Nilotinib 300 mg twice daily	80	55	77	66	54	0.7	93.7
	Nilotinib 400 mg twice daily	78	51	77	63	52	1.1	96.2
	Imatinib 400 mg	65	27	60	42	31	4.2	91.7
BFORE (*N* = 536)	Bosutinib 400 mg daily	77.2	47.2	73.9	58.2	47.4	2.2	94.5
	Imatinib 400 mg daily	66.4	36.9	64.6	48.1	36.6	2.6	94.6

First-line TKI options for CP CML

Imatinib mesylate

The promise of targeted therapy for CML was realized with the regulatory approval of the first small-molecule TKI for cancer, imatinib mesylate, in May 2001. Imatinib binds the adenosine triphosphate binding site in the catalytic domain of the BCR-ABL1 oncoprotein and inhibits the BCR-ABL1 TK activity. This interaction prevents the transfer of phosphate groups to tyrosine residues on substrate molecules involved in downstream signal transduction pathways. The drug also inhibits the kinase activity of normal ABL1, ABL2, PDGFRA, PDGFRB, and KIT. Generic imatinib is now available.

The pivotal phase 3 study comparing imatinib to the combination of interferon alpha (IFNα) and cytarabine (IRIS study) demonstrated the superiority of imatinib over IFNα plus cytarabine, with higher rates of CHR, MCyR, and CCyR; freedom from progression to AP or BP CML; and better tolerance of therapy. With a median follow-up of 19 months, this study reported estimated rates of CCyR of 76.2% for imatinib-treated patients versus 14.5% for patients receiving IFNα and cytarabine.

The 10-year follow-up report provided long-term efficacy and safety data on 553 patients who were randomized to the first-line imatinib arm of the IRIS study. At the end of the trial, the rate of CCyR at any time was 82.8%. Among patients with evaluable molecular data at 10 years (*N* = 204/516), 93.1% had achieved MMR and 63.2% MR4.5. The estimated OS at 10 years was 91.1% versus 85.3% in patients with and without MMR, respectively, at 12 months. There were low yearly rates of progression to AP or BP CML in years 4 to 8 after starting imatinib treatment (0.9%, 0.5%, 0%, 0%, and 0.4%). Among the imatinib-treated group, 6.9% had progression to AP or BP and the estimated rate of freedom from progression to AP or BP at 10 years was 92.1%. Estimated OS at 10 years was worse in patients with a high Sokal risk score as compared to those with an intermediate or low risk score (68.8% versus 80.3% versus 89.9%, respectively). Among patients randomly assigned to imatinib, 15.9% of patients discontinued study treatment due to unsatisfactory therapeutic effect and 6.9% due to adverse events.

Despite impressive results with imatinib, several attempts have been made to improve response rates and decrease resistance in newly diagnosed patients through the use of higher doses of imatinib (600-800 mg/d). Numerous trials have been completed using higher doses of imatinib or combinations of imatinib plus IFNα or cytosine arabinoside (Ara-C); however, in the end, none resulted in better outcomes than imatinib 400 mg daily. For this reason, at this time, neither high-dose imatinib nor imatinib in combination with IFN are recommended frontline treatments and would be considered investigational. It is important to note though that several studies have demonstrated a faster and deeper responses with higher dose imatinib possibly equating a higher dose imatinib with second-generation TKIs.

Toxicity

Adverse effects include myelosuppression (in particular neutropenia), fatigue, gastrointestinal disturbances such as nausea and diarrhea, rash, edema (periorbital and peripheral), and muscle cramps. Long-term consequences may rarely include hypophosphatemia and a decrease in bone mineral density. Cardiotoxicity, including congestive heart failure, is rare. For children, unique toxicities exist, including growth abnormalities, especially in prepubertal children. These effects may be due to effects on the growth hormone/IGF-1 axis. The long-term safety profile of imatinib remains excellent. In many patients who

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

experience unacceptable adverse effects, transient dose reduction or treatment interruption with supportive care allows patients to resolve adverse effects and resume full-dose or modified therapy.

Dasatinib

Dasatinib, which lacks structural similarity to imatinib, has activity against Src family kinases in addition to ABL kinases. Dasatinib does not rely on a conformational change of ABL for binding and thus appears to be less susceptible to the development of resistant kinase domain mutations that alter ABL conformation. Dasatinib is approved for the treatment of adults with newly diagnosed CP CML and CP CML with resistance or intolerance to prior therapy.

Data from the 5-year follow-ups of patients enrolled in the phase 3 randomized, open-label trial Dasatinib versus Imatinib study in Treatment-Naive CML-Chronic Phase (DASISION) showed that CCyR rates between dasatinib- and imatinib-treated patients were 87% versus 83%, but the median time to CCyR was shorter in dasatinib-treated patients (3.1 months versus 5.8 months). The cumulative rates of MMR and deeper responses including MR4 and MR4.5 were higher for dasatinib as compared to imatinib. Transformation to AP or BP occurred in 5% and 7% of patients in the dasatinib and imatinib arms, respectively. More imatinib-treated patients died because of CML-related causes ($N = 17$) compared with dasatinib-treated patients ($N = 9$); however, no statistically significant difference was noted in the 5-year OS between dasatinib- and imatinib-treated patients (91% versus 90%, respectively) (hazard ratio [HR], 1.01; 95% CI, 0.58-1.73). In patients who achieved EMR (*BCR-ABL1* ≤10%) at 3 months (dasatinib, 84%; imatinib, 64%), improvements in PFS and OS and lower rates of transformation to AP/BP were reported compared with patients not achieving EMR at 3 months. These improved PFS and OS were noted irrespective of the TKI patients were receiving. Similar results were seen in another randomized trial of imatinib 400 mg daily versus dasatinib 100 mg daily. With dasatinib, patients had faster deeper responses, higher rate of hematological toxicity with no difference in overall survival. The higher rates of hematological toxicity may be abrogated by using a lower dose up front as are detailed in the following.

Toxicity

Adverse effects of dasatinib include myelosuppression, in particular neutropenia and thrombocytopenia. Unique toxicities include pleural effusion, suggesting that patients with lung disease, congestive heart failure, and hypertension may not tolerate this agent. The incidence of pleural effusion increases with increasing dose and age. With a 7-year follow-up of the dose-optimization study, the incidence of pleural effusion was 28% at 100 mg once daily versus 35% for the other dose groups and was similar to the incidence reported in updates at 5 years from the first-line DASISION study. Pleural effusions are managed with treatment interruptions, dose reductions and in some instances steroids. In clinical studies, approximately 6% of patients discontinued dasatinib secondary to pleural effusions. Other unique, but uncommon, toxicities include pulmonary hypertension and platelet dysfunction. The incidence of pulmonary hypertension is reported to be ≤5% and often occurs concurrently with pleural effusion. A recent retrospective review of 41 cases suggests pulmonary hypertension may be reversible, in part, with dasatinib cessation. Lastly, reports suggest dasatinib use has effects on growth in children similar to imatinib.

Nilotinib

Nilotinib is a structural derivative of imatinib that is a 30-fold more potent inhibitor of BCR-ABL1 activity and has been approved the treatment of newly diagnosed patients with CP CML and CP CML in adult patients resistant or intolerant to prior therapy. Its United States Food and Drug Administration (FDA) approval was expanded in 2017 to include that patients with newly diagnosed Ph^+ CML in the chronic phase and resistant or intolerant Ph^+ CML-CP patients who have achieved a sustained molecular response (MR4.5) may be considered for discontinuation after at least three of nilotinib therapy.

In the phase 3 randomized, open-label trial Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd), nilotinib (300 mg twice daily or 400 mg twice daily) was compared with 400 mg/d of imatinib. CML patients on 300 mg or 400 mg twice daily of nilotinib had superior CCyR in 12 months compared with patients treated with imatinib 400 mg/d (80% and 78% versus 65%). The time to progression to AP or BP CML was better with the nilotinib-treated patients. Data from the 36-month follow-up showed the superiority of nilotinib 300 mg or 400 mg twice daily compared with 400 mg once daily of imatinib in terms of rates of MMR (73% and 70% versus 53%), MR4 (50% and 44% versus 26%), rates of AP/BP CML progression (2 patients [0.7%] and 3 patients [1.1%] versus 12 patients [4.2%]), and incidence of mutations (11 patients in each nilotinib arm versus 21 in imatinib-treated patients). The

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

estimated 3-year OS was not statistically significantly different among the three groups (95%, 97%, and 94%), but the authors reported better OS for those treated with nilotinib compared with those treated with imatinib, if only CML-related deaths were considered (98.1% versus 98.5% versus 95.2%; HR, 0.35; $P = 0.0356$). By 5 years, more than one-half of all patients in each nilotinib arm (300 mg twice daily, 54%; 400 mg twice daily, 52%) achieved MR4.5 compared with 31% of patients in the imatinib arm. EMR rates were also higher in nilotinib-treated patients. A benefit of nilotinib was observed across all Sokal risk groups.

Toxicity

Unique toxicities associated with nilotinib use include hyperglycemia, hyperlipasemia, hyperbilirubinemia, pancreatitis, and QT interval prolongation. Increasing recognition of vascular toxicities associated with nilotinib use is emerging, including cerebrovascular, cardiovascular, and peripheral arterial occlusive diseases, which have been reported in patients with or without cardiovascular risk factors. At the 10-year follow-up of the ENESTnd study, the cumulative rate of all cardiovascular events was 23.5%, 16.5%, and 3.6% for patients receiving nilotinib 400 mg twice daily, nilotinib 300 mg twice daily, and imatinib 400 mg daily, respectively. It was also noted that the cumulative frequency of events increased over time on nilotinib treatment. As a consequence, nilotinib should be used with extreme caution in individuals with diabetes mellitus, cardiovascular disease, or metabolic syndrome. The mechanism of these events remains elusive, but recent studies suggest that vascular endothelial cells may play a role. Additionally, reports have suggested the increased risk of hyperglycemia with nilotinib, as well as increasing body mass index and hyperlipidemia contribute to the increased risk of vascular events seen in nilotinib-treated individuals. Recent reviews have recommended increased monitoring of lipids and hemoglobin A1c at yearly to twice-yearly intervals in nilotinib-treated patients.

Bosutinib

Bosutinib, a dual Src/Abl kinase inhibitor, is FDA-approved for the frontline treatment of CP CML based on results of the phase 3 randomized Bosutinib Trial in First-Line Chronic Myelogenous Leukemia Treatment (BFORE) trial, a follow-up study to the phase 3 Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial, which compared bosutinib with imatinib in newly diagnosed CP CML. The BELA study did not achieve its primary end point, the rate of CCyR at 12 months, but did demonstrate a significant improvement in MMR rate at 12 months (41% versus 27%, bosutinib versus imatinib, respectively; $P = 0.001$). There were also fewer on-treatment transformations to AP or BP CML and fewer CML-related deaths with bosutinib. Because bosutinib given at 500 mg orally daily on the BELA study resulted in more frequent gastrointestinal and liver-related toxicities as compared to imatinib-treated patients, the BFORE study randomized 536 patients to bosutinib at 400 mg daily versus imatinib at 400 mg daily. The median dose intensity was 392 mg daily for bosutinib and 400 mg daily for imatinib. At 12 months, MMR rates were significantly higher in bosutinib-treated patients as compared to imatinib-treated patients (47.2% versus 36.9%, respectively; $P = 0.02$). This difference was even more pronounced for patients with high Sokal risk scores. The rates of MMR in patients with high Sokal risk scores was 34.0% versus 16.7% for bosutinib versus imatinib, respectively. CCyR rates at 12 months were higher in patients receiving bosutinib as compared to imatinib (77.2% versus 66.4%, respectively). EMR (*BCR-ABL1* transcripts ≤10% at 3 months) was achieved in a greater proportion of patients receiving bosutinib as compared to imatinib (75.2% versus 57.3%, respectively), and deeper molecular responses at 3, 6, 9, and 12 months were seen more frequently in bosutinib-treated patients. Similar to earlier studies of dasatinib and nilotinib, no statistically significant difference in OS or EFS was observed in patients receiving bosutinib as compared to imatinib. Four patients (1.6%) receiving bosutinib and six patients (2.5%) receiving imatinib experienced disease progression to AP or BP.

Toxicity

Similar to other TKIs, bosutinib is associated with myelosuppression, in particular thrombocytopenia. Unique toxicities associated with bosutinib use are primarily gastrointestinal, including diarrhea, nausea, vomiting, pancreatitis and transaminitis. In patients treated with second- or third-line bosutinib, diarrhea was common (86% and 83%, respectively), but the incidence of grade 3/4 diarrhea was low (10% and 9%, respectively). The most common grade 3/4 toxicity in resistant or intolerant patients was thrombocytopenia (25%). In the first-line BFORE study, the most common adverse events of all grades in bosutinib-treated patients were diarrhea (70.1%), nausea (35.1%), thrombocytopenia (35.1%), increased alanine aminotransferase (30.6%), and increased aspartate aminotransferase (22.8%). Similar to studies of bosutinib in intolerant or resistant patients, diarrhea was primarily grades 1 and 2, with only 7.8% of first-line bosutinib-treated patients having grade 3 diarrhea. Diarrhea symptoms responded to dose

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

adjustments and improved in many patients over time. The incidence of pleural effusion, cardiovascular events, and peripheral vascular events was low.

Management of chronic-phase CML resistant or intolerant to prior TKI

The choice of TKI for patients with CP CML who are resistant or intolerant to a TKI depends on the presence of mutations, comorbidities, and adherence. For patients with intolerance to a TKI, changing therapy usually results in resolution of those symptoms. There is very little cross intolerance between TKIs. In patients who have resistant disease (not meeting treatment milestones) a thorough evaluation should be performed prior to switching TKI. This would include assessing for adherence, bone marrow biopsy, drug interactions and BCR-ABL1 mutation analysis. Lack of adherence is a common cause for patients not meeting treatment milestones and will be discussed later in detail. A bone marrow biopsy is important to evaluate the phase of the disease. Certain mutations are more sensitive to specific TKIs. For example, ponatinib is the only drug effective against CML harboring the T315I mutation. See Table 16-1 for TKI choice in the presence of specific BCR-ABL1 mutations. Similar to first-line therapy, the presence of comorbidities guides the choice of therapy. However, options become more limited and the threshold for accepting toxicities becomes lower, especially in patients with resistant disease.

Dasatinib second-line or later therapy in patients with CP CML

Dasatinib was first investigated in CML patients with resistance or intolerance to imatinib in a series of phase 2 trials called START (SRC/ABL Tyrosine kinase inhibition Activity Research Trials). The START-C study was a single-arm study of dasatinib at 70 mg orally twice daily, and START-R was a randomized parallel-arm study of dasatinib versus high-dose imatinib. For START-C, MCyR and CCyR rates were 62% and 53%, respectively, with a minimum follow-up of 24 months. Results for START-R were similar. Additionally, START-R demonstrated superior MCyR and CCyR rates for the use of dasatinib rather than an increased dose of imatinib. Notably, for both studies, the median daily dose was ~100 mg daily due to dose reductions. Consequently, a phase 3 dose-optimization study randomized patients 1:1:1:1 between four dasatinib treatment groups: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Seven-year follow-up from this study for patients receiving dasatinib at 100 mg daily demonstrated sustained benefit, with MMR, PFS, and OS rates of 46%, 42%, and 65%, respectively. Similar to first-line studies, EMR was associated with improved PFS and OS. Across dasatinib studies for CP, as well as advanced-phase, treatment responses were limited for patients with T315I or F317L mutations, and possibly lower response rates were seen in patients with Q252H, E255K, or E355G mutations. Dasatinib has also been evaluated as third-line therapy in patients who have received imatinib followed by nilotinib. In a study by Garg et al, of the 16 patients with chronic-phase CML treated with dasatinib as third-line therapy, 31% and 13% achieved CCyR and MMR, respectively.

Nilotinib second-line or later therapy in patients with CP CML

Like dasatinib, nilotinib has also demonstrated significant clinical activity and an acceptable safety and tolerability profile in patients with imatinib-resistant or -intolerant CP CML. Four-year follow-up from an international phase 2 study of CP CML in resistant/intolerant patients treated with nilotinib revealed that 59% achieved MCyR and 45% CCyR, and OS was estimated at 78%. Deeper responses at 3 and 6 months correlated with improved later outcomes, including OS. In an expanded-access, open-label study of 1422 patients who had progressed on prior imatinib, CCyR was attained in 34% of nilotinib-treated patients. In another study of patients in CCyR, but with detectable *BCR-ABL1* transcripts after more than 2 years on imatinib, patients randomized to nilotinib had higher rates of undetectable *BCR-ABL1* compared to those randomized to imatinib at 2 years (22.1% versus 8.7%, $P = 0.0087$); deeper responses (MR4.5) at 2 years were also more commonly observed in nilotinib-treated patients.

In an international phase 2 trial of nilotinib as third-line therapy, 39 patients with chronic-phase CML were enrolled. The rate of MCyR was 43%, and 24% achieved CCyR. The estimated 18-month PFS and OS were 59% and 86%, respectively.

Bosutinib second-line or later therapy in patients with CP CML

Bosutinib was approved for the treatment of adult patients with CP, AP, or BP CML who are resistant or intolerant to imatinib, based on a single-arm, open-label multicenter study of CP, AP, and BP CML patients who received at least one prior TKI (either imatinib or imatinib followed by nilotinib or dasatinib). A total of 546 patients were enrolled, of whom 73% were imatinib resistant and 27% were imatinib intolerant. Among 284 CP CML patients, cumulative MCyR and CCyR rates were 58% and 46%,

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

respectively, by year 2 and 60% and 50%, respectively, by year 5. The cumulative MMR rate was 42%. Estimated OS was 91% at year 2 and 84% at year 5. The most frequent mutations newly emerging on bosutinib included T315I, V299L, and M244V. Specifically focusing on 119 patients receiving bosutinib in the third- or fourth-line setting after imatinib and nilotinib or dasatinib, or both, the cumulative 4-year MCyR rate was 40%, and 26% attained CCyR. At 4 years, the cumulative incidence of on-treatment progression and death was 24%.

Ponatinib

Ponatinib is FDA-approved for patients with CP CML with resistance or intolerance to at least two prior kinase inhibitors or with a T315I mutation. Patients with accelerated-phase or blast-phase CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph^+ ALL) for whom no other kinase inhibitors are indicated or with a T315I mutation.

The T315I mutation results in resistance to TKI therapy due to a threonine/isoleucine substitution resulting in steric inhibition, which prevents binding to and inhibition of the kinase domain. Ponatinib, a third-generation oral pan-BCR-ABL1 TKI, has shown significant activity in CML patients with T315I mutations or who are resistant to multiple TKIs. In the phase 2 Ponatinib Ph-Positive Acute Lymphoblastic Leukemia and CML Evaluation (PACE) trial, refractory CP, AP, and BP CML or Ph^+ ALL patients resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation, were treated with ponatinib (45 mg orally once daily). A total of 88% of the patients in the cohort had resistance to either dasatinib or nilotinib. Among 267 CP CML patients, 56% attained MCyR (51% with resistance or intolerance of dasatinib or nilotinib and 70% with the T315I mutation), 46% achieved CCyR (40% of those with resistance/intolerance and 66% with the T315I mutation, respectively), and 34% attained MMR (27% of those with resistance/intolerance and 56% with the T315I mutation, respectively). The median time to MCyR was rapid at 2.8 months, and the rate of sustained MCyR at 12 months was 91%. A recent meta-analysis of clinical trials of nilotinib, dasatinib, bosutinib, and ponatinib in the resistant/intolerant setting suggested that ponatinib may have increased efficacy in CP CML after failure of second-generation tyrosine kinase inhibitors. Estimated probabilities of CCyR with treatment with another second-generation TKI after second-generation TKI failure ranged from 22% to 26% for second-generation TKIs, as compared with 50%-60% for ponatinib. Based on these promising observations, the Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia (EPIC) study randomized patients to receive oral ponatinib (45 mg) or imatinib (400 mg) once daily. Due to safety concerns emerging from phase 1 and 2 trials, this study was terminated early and did not meet its primary end point. Secondary analyses, however, demonstrated that more patients treated with ponatinib as compared to imatinib achieved MMR or MR4.5 at 3 months (31% versus 3% and 5% versus 0%, respectively).

Toxicity

Toxicities associated with ponatinib, primarily vascular, have limited its use. In the PACE study, the most common adverse events included thrombocytopenia, rash, dry skin, and abdominal pain. Updates to ponatinib labeling now report that arterial occlusive events have occurred in at least 26% of ponatinib-treated patients, including myocardial infarction, stroke, stenosis of large arterial vessels of the brain, and severe peripheral vascular disease, which have also occurred in younger individuals. Among 154 patients treated in the EPIC study, 7% of ponatinib-treated patients developed arterial occlusive events compared to 2% in the imatinib group, and the median time to onset was ~4 months. Because of these adverse events, ponatinib sales were briefly suspended in the United States. Ponatinib was formerly part of a risk evaluation and mitigation strategy in the United States with careful monitoring recommended. The mechanism of ponatinib vascular toxicity is not fully understood, but ponatinib treatment resulted in hypertension in 26% of patients in the PACE study. The OPTIC study (Optimizing Ponatinib Treatment In CML) evaluated the starting ponatinib dose safety and efficacy. Patients were randomized to ponatinib 45 mg versus 30 mg versus 15 mg. Dose reduction to 15 mg was indicated for patients achieving ≤1% BCR-ABL1^{IS}. At 12 months, 39%, 27%, and 26% achieved ≤1% BCR-ABL1^{IS} in the 45, 30, and 15 mg cohorts, respectively. Arterial occlusive events were reported in 5%, 4%, and 1% in the 45mg, 30 mg, and 15 mg cohorts. respectively.

Consequently, the use of ponatinib requires a careful assessment of risk and benefit in individual patients, and further study is needed to delineate more clearly its use outside of T315I- mutated CML, as well as the appropriate dosing of ponatinib.

Accelerated-phase CML

The AP CML is accompanied by the acquisition of additional molecular lesions, genomic instability, and progressive impairment of myeloid cell differentiation. This latter feature leads to the accumulation of immature precursors

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

and blasts in the marrow, blood, and extramedullary tissue. The various definitions of AP are shown in Table 16-2. It should be noted, however, that the MD Anderson and ELN definitions have been used to define CP and AP CML for most clinical studies reported in this chapter. Although, the definitions are generally similar, the proportions of blasts in AP are 15% to 29% and 10% to 19% in the ELN/MD Anderson and WHO criteria, respectively. In the absence of effective therapy with either TKI or allogeneic SCT, the median survival from the onset of AP, historically, is only 12 to 18 months. Death occurs predominantly because of transformation to BP with the associated life-threatening complications of marked leukocytosis and complete failure of normal hematopoiesis. It has also been observed that the proportion of pediatric patients diagnosed with AP or BP is higher than that for adult patients, although the reasons for this observation are unclear. Although AP patients do not share the generally good prognosis of CP patients in the era of TKIs, studies of newly diagnosed AP patients, as defined by ELN criteria, have identified subsets of patients who may respond well to first-line TKI therapy, which is discussed in a later section.

Management of patients with accelerated-phase CML

For patients with de novo AP CML, defined using ELN criteria, subsets of patients who may respond well to first-line imatinib have been identified. Patients with AP CML, as defined solely by hematological parameters, as compared to patients with additional cytogenetic aberrations and hematological parameters, had improved rates of major and complete cytogenetic response (94% versus 40% and 81% versus 30%, respectively) and failure-free survival (87.5% versus 15%, respectively). Hematological parameters included any of the following features: at least 15% to <30% blasts in peripheral blood or bone marrow, >30% blasts plus promyelocytes provided that <30% blasts are present, at least 20% peripheral blood basophils or platelets less than 100×10^9/L unrelated to therapy.

In general, a second-generation TKI is recommended for patients with AP CML. In a small retrospective study, patients who received a second-generation TKI had better outcome compared to patients who received imatinib. For patients who progress to accelerated-phase while on TKI therapy, TKI therapy followed by stem cell transplantation for eligible patients is indicated.

With 2 years of follow-up, nilotinib, at a dose of 400 mg orally twice daily in patients with AP CML, led to CHR, MCyR, CCyR, and MMR in 31%, 32%, 21%, and 11% of patients, respectively. The 24-month overall survival rate was 70%. Nilotinib is approved for use in AP CML with resistance or intolerance to other therapy. Dasatinib, at a dose of 140 mg/d, led to CHR, MCyR, and CCyR in 45%, 39%, and 32% of patients with AP CML, respectively. Responses were achieved in imatinib-resistant and -intolerant patients. The 12-month PFS and OS rates were 66% and 82%, respectively. In another study, a subgroup of patients with AP CML randomized to 140 mg once daily or 70 mg twice daily experienced comparable rates of major hematologic response (MHR; 66% versus 68%) and MCyR (39% versus 43%), but once-daily dosing was associated with a more favorable safety profile. Bosutinib is also approved for patients with AP CML. With ≥4 years of follow-up the CHR and MCyR rates for patients receiving bosutinib were 57% and 40%, respectively. In a study of ponatinib in patients with AP CML, 55% achieved MHR, 39% achieved MCyR, 24% achieved CCyR, and 16% achieved MMR (Table 16-6).

Blast-phase CML

Progression of CML to acute leukemia, synonymous with "blast-phase" or "blast crisis," evolves most commonly from a preceding AP and is reached when the proportion of blasts in the blood or marrow is >20% (Table 16-2) (WHO criteria). It should be noted, however, that the majority of clinical trials used ELN/MD Anderson criteria to define BP (≥30% blasts). Data from the IRIS study demonstrated that the risk for progression to AP or BP is highest in the first 4 years of imatinib treatment and reported annual rates of progression in years 1-4 of 1.5%, 2.8%, 1.6%, and 0.9%, respectively. Myeloid lineage markers (eg, CD33, CD13, CD14, and CD15) are expressed by the blast cells in more than one-half of the cases of BP CML. Up to one-third express B cell–precursor lymphoid markers (eg, CD10, CD19, and CD20). Undifferentiated acute leukemia cases displaying both myeloid and lymphoid cell surface markers account for the remainder. Most CML cases express the p210 *BCR-ABL1* gene product, and only rare cases are associated with p190 *BCR-ABL1* alone. Thus, a case of Ph-positive ALL that subsequently is found to be associated with p210 *BCR-ABL1* might actually represent previously unrecognized CML presenting in lymphoid BP. That said, the diagnosis of lymphoid BP typically relies on documentation of a preceding CP. The features of BP CML are summarized in Table 16-2. Although BCR-ABL1 is still an important driver, BP cells acquire additional cytogenetic and molecular changes contributing to either poor TKI response or rapid loss of response. ACAs in addition to t(9;22) are found in 65%

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Table 16-6 Key findings in accelerated AP CML studies

	N	Patient characteristics	Follow-up (mo)	CHR (%)	CCyR (%)	MMR (%)	PFS (y)	OS (y)
Imatinib	176	No prior TKI	41	82	43	50	NR	53% (4)
Nilotinib	137	Second-line after imatinib Imatinib resistant: 109 (80%)	24	31	21	11*	33% (2)	70% (2)
Dasatinib	174	Imatinib only Resistant: 161 (96)	14	45	32	NR	66% (1)	82% (1)
Bosutinib	79	Imatinib only: 29 (59) ≥2 TKIs: 25 (32)	28.4	33	31	NR	NR	59% (4)
Ponatinib	85	≥2 TKIs: 80 (94)	32.3		31	22	22% (5)	49% (5)

NR, Not reported.

*Data available for 109 patients.

to 80% of cases of BP. Unfortunately, even in the era of TKIs, outcomes for BP CML remain poor, with median survival ranging between 7 and 11 months. Two key, independent predictors of worse overall survival are (1) >50% of circulating white blood cells composed of blasts and (2) the acquisition of additional cytogenetic abnormalities. Deaths usually are due to metabolic derangements, infection, bleeding, and extramedullary leukemic infiltration.

Management of patients with blast-phase CML

The management of patients with blast-phase CML depends on whether the disease has progressed to myeloid or lymphoid blast crisis, presence of mutations, comorbidities, and overall performance status of the patient. The goal of treatment is to get the patient back to chronic phase and proceed to stem cell transplantation.

TKIs can transiently control CML blast phase in a proportion of patients and serves as a bridge to SCT in patients who are candidates for SCT. We recommend the use of second- or third-generation TKIs, although imatinib is also effective. Imatinib induced overall hematologic responses in ~50% of study subjects, 8% to 21% achieved CHRs, and ~30% achieved stable or sustained hematologic responses (lasting ~4 weeks). MCyRs occurred in 16% of patients, and CCyRs occurred in 7% of patients. The median overall survival for patients who achieved a sustained hematologic response was 19 months. Myelosuppression was common, and nonhematologic toxicities were mild to moderate.

Two-year follow-up from a study of patients with BP CML treated with either dasatinib 140 mg daily or 70 mg twice daily suggested that once-daily dosing had comparable efficacy and better tolerability. In those with myeloid BP CML treated with once-daily dasatinib, the MHR was 28%, MCyR was 25%, and OS at 24 months was 24%. For those with lymphoid BP CML, corresponding rates were 42%, 50%, and 21%, respectively. Dasatinib is approved for AP and myeloid or lymphoid BP CML with resistance or intolerance to other therapy.

Bosutinib has been approved for AP and BP CML with resistance or intolerance to prior therapy. Updates of advanced-phase patients with ≥4 years of follow-up demonstrated that among BP patients, 28% and 37% attained overall hematologic response and MCyR, respectively. Lastly, ponatinib is an option for those with advanced disease and intolerance/resistance to prior therapy. Among patients with BP CML, 31% achieved MHR, 23% achieved MCyR, and 18% achieved CCyR.

Overall, outcomes for BP CML remain dismal even in the era of TKIs, although a subset of BP CML patients, as defined by WHO criteria with blast percentages of 20% to 29%, may have outcomes more similar to AP patients. A recent retrospective review of 477 BP patients attempted to identify characteristics or prognostic factors associated with outcomes. Among this group, 72% had received prior TKI therapy before progression. Median OS in this group was 12 months, and median failure-free survival was 5 months. As initial therapy for BP, 35% received TKI alone, 46% TKI with chemotherapy, and 19% non-TKI therapy. Factors that predicted for increased risk of death in multivariate analysis included myeloid immunophenotype, prior TKI, age ≥58 years, lactate dehydrogenase level ≥1227 IU/L, platelet count <102,000/μL, no history of stem cell transplantation, transition to BP from CP/AP, and the presence of chromosome 15 aberrations. Additionally, as reported in other studies, achievement of major hematologic response and/or CCyR to first-line treatment was predictive of improved OS. This study also suggested that combination chemotherapy with TKI followed by SCT conferred the best outcome. Although in lymphoid BP chemotherapy with TKI can be more effective, whether combination chemotherapy and TKI results in improved outcomes in myeloid BP is unclear. Therapies used in the treatment of patients with relapsed refractory

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Ph^+ ALL such as blinatumomab, inotuzumab, combination chemotherapy are also effective in the patients with CML in lymphoid blast crisis. For patients with myeloid blast crisis, chemotherapy such as FLAG-IDA or decitabine in combination with TKI may be used.

Adherence and treatment failure

Another important, but difficult to quantify, contributor to treatment failure is poor therapy adherence. In general, adherence should be continually addressed and specifically whenever response milestones are not met. Although it is difficult to compare studies head-to-head given the differences in assessment of adherence (eg, chart review versus pill counts versus electronic devices to measure bottle opening versus review of healthcare databases), the rates of nonadherence at 25%-35% are similar in many of these studies. Definitions for nonadherence on imatinib included the use of ≤85% or 90% of prescribed drug. The ADAGIO study examined adherence in 169 patients in Belgium and observed that approximately one third of patients were nonadherent and only 14.2% of patients were 100% adherent with prescribed imatinib. Nonadherence was associated with poorer cytogenetic response. In another study of 87 patients treated at Hammersmith Hospital in London, United Kingdom, patients with adherence rates of ≤85% had an increased probability of losing CCyR (26.8% versus 1.5%).

The ADAGIO study identified several factors that adversely impacted adherence, including age, living alone, dose of imatinib, male sex, length of time from diagnosis to treatment, and length of imatinib treatment. Factors that positively influenced adherence included increased knowledge about CML disease and treatment, at least a secondary education, and taking other medications chronically. A Hammersmith Hospital study of patient adherence further explored issues and behavior contributing to nonadherence. The most common reason for nonintentional nonadherence was forgetfulness, but the most common reason for intentional nonadherence was to minimize side effects. Notably, many patients did not think missing doses would significantly impact their response, and patients relied upon their treating healthcare teams to comment on the impact of nonadherence on-treatment responses. These observations suggest that a proactive approach may improve adherence. Suggestions include nursing or pharmacist phone calls or visits to assess for adverse effects, dispensing pill boxes to assist taking pills on schedule, recommendations to link TKI use to a regular scheduled daily activity, cell phone alerts, and taking particular care to discuss these issues with patients who have risk factors for nonadherence. Of note, an early study reported that short *BCR-ABL1* transcript doubling time could distinguish nonadherence from resistance and may assist physicians in recognizing nonadherent patients.

Discontinuation of TKI therapy and dose deescalation

Stopping TKI therapy with the goal of TFR is now part of current treatment recommendations and guidelines. Despite early concerns that imatinib and other TKIs do not target CML stem cells and discontinuation would be risky, a considerable body of work over the past decade supports the safety of this intervention. The initial studies in France (Stop Imatinib [STIM]) and Australia (TWISTER) enrolled adult patients who had been treated with imatinib and had achieved deep and durable responses, defined as a >5-log reduction in *BCR-ABL1* transcript levels, for >2 years. TKI therapy was restarted at the time of molecular recurrence. Of 100 patients in the STIM study with a median follow-up of 77 months (range, 9-95 months), 38% remained in molecular response at 60 months. Molecular recurrence was most frequent within 6 months of stopping imatinib therapy. Treatment was restarted in 57 of 61 patients with molecular recurrence, and 55 patients achieved a >5-log reduction in *BCR-ABL1* transcript levels at a median time of 4 months (range, 1-16 months). TWISTER reported similar TFR rates (47%) and also observed that molecular relapse, when it occurred, occurred early. Reassuringly all patients regained deep molecular responses upon restarting therapy. Subsequent studies, such as A-STIM, also investigated the possibility of stopping imatinib in patients with less deep molecular responses and more clearly defined when therapy should be restarted, namely at the time of loss of MMR. Notably, fluctuations of *BCR-ABL1* transcript levels below the MMR threshold were observed in 31% of patients after discontinuation.

ELN has recently conducted a large multicenter study of treatment discontinuation in patients who have received TKI for at least 3 years and have achieved and sustained MR4 for at least 1 year (EURO-SKI). The results show similar relapse-free survivals as earlier studies. Factors predictive of successful discontinuation were duration of imatinib treatment greater than a median of 5.8 years and duration of deep molecular response of 3.1 years or longer. The LAST trial (Life After Stopping Tyrosine kinase inhibitors) was recently reported. In that study, 172 patients with a sustained deep molecular response discontinued therapy. At study enrollment, 59.3%, 22.7%, 15.7%, and 2.3% were on imatinib, nilotinib, dasatinib, and bosutinib respectively. Treatment was restarted for loss of MMR. Overall, 61% maintained TFR with a median follow-up of 3 years. Undetectable BCR-ABL1 by digital

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

PCR was highly predictive of successful TFR. Of the 87 patients with undetectable BCR-ABL1 by both RQ-PCR and digital PCR at time of discontinuation only 10.3% (9 of 87) patients lost MMR compared to 64.3% for those with undetectable BCR-ABL1 transcripts by RQ-PCR but detectable by digital PCR. Of the patients who maintained TFR at 12 months, 80%, 35%, 88%, and 5% had clinically meaningful improvement in fatigue, diarrhea, sleep disturbance, and pain, respectively.

Two studies have examined stopping dasatinib or nilotinib after imatinib intolerance or resistance. Results are similar to those of stopping imatinib, but both studies reported higher rates of molecular recurrence in patients with resistance to imatinib. ENESTfreedom enrolled 215 patients who had achieved MR4.5 and had received a minimum of 2 years treatment with nilotinib and treated them with standard-dose nilotinib for a further year. At that point, 190 patients discontinued nilotinib, and 48 weeks later, 98 of 190 patients (51.6%) remained in MMR without treatment reinitiation. Other strategies to improve the numbers of patients eligible for TFR include an attempt of second TFR. However, the success rate is low. Trials of adding ruxolitinib or asciminib in order to achieve a higher success rate of TFR are ongoing. Recommendations for stopping TKI outside of the context of clinical trials have been endorsed by organizations such as NCCN and the ELN (Table 16-7) based on published recommendations for management. Access to high-quality RT-QPCR monitoring and monthly estimations of *BCR-ABL1* transcript levels, particularly in the first 6 to 12 months, is mandatory. Patients should have an easily quantifiable transcript type amenable to standardized technology, have generally achieved optimal responses according to ELN, have been treated for at least 3 years, and have deep molecular response of MR4 or better for at least 2 years. Approximately 25% of patients experience a "withdrawal syndrome" on stopping TKI, which is manifested by musculoskeletal pain occurring 1 to 6 weeks after discontinuation and/or generalized pruritus. The pain can resemble polymyalgia rheumatica or cause arthralgia, particularly of hips, shoulders, hands, and feet. It usually resolves spontaneously, although this might take many weeks and in some cases months.

An alternative approach was taken in the UK DESTINY study, which explored the benefit of an initial 12-month period of a 50% dose reduction from standard doses of imatinib, nilotinib, or dasatinib. Eligibility criteria required a minimum treatment period of 3 years and included patients in MMR, in addition to those in MR4 or deeper for at least 12 months. The trigger for restarting TKI was loss of MMR. After 1 year of dose reduction, recurrence was significantly lower in the MR4 cohort (3 [2%; 90% CI, 0.2-4.8] of 121 evaluable patients) than in the MMR cohort (9 [19%; 90% CI, 9.5-28.0] of 48 evaluable patients; HR, 0.12; 90% CI, 0.04-0.37; $P = 0.0007$).

Table 16-7 Criteria for TKI cessation

ELN 2020 recommendations
Mandatory
CML in CP only
Motivated patient with structured communication
Access to high-quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
Patients agreement to more frequent monitoring after stopping treatment. This means monthly checks for the first 6 months, every 2 months for months 6-12, and every 3 months thereafter
Minimal (stop allowed)
First-line therapy or second-line therapy if intolerance was the only reason for changing TKI
Typical e13a2 or e14a2 BCR-ABL1 transcripts
Duration of TKI therapy >5 years (>4 years for 2GTKI)
Duration of DMR (MR4 or better) >2 years
No prior treatment failure
Optimal (stop recommended for consideration)
Duration of TKI therapy >5 years
Duration of DMR >3 years of MR4
Duration of DMR >2 years if MR4.5
NCCN Guidelines Version 3.2022
Must meet all criteria
Age ≥18 years
Chronic-phase CML. No prior history of accelerated of blast-phase CML
On approved TKI therapy for at least 3 years
Prior evidence of quantifiable BCR-ABL1 transcript
Stable molecular response (MR4; BCR-ABL1 ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart
Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (BCR-ABL1 ≤0.0032% IS) and that provides results within 2 weeks
Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7-12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; BCR-ABL1 ≤0.1% IS)
Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is reestablished, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Dose deescalation is another strategy to improve patients quality of life. In a study by the MD Anderson Cancer Center (MDACC), patients with newly diagnosed chronic-phase CML started with dasatinib 50 mg daily instead of the FDA-approved dose of 100 mg. In that phase 2 study the rates of responses were similar or even higher when compared to historical controls. The MMR rate at 12 months was 81%, which appears higher than the MMR rate at 12 months in the DASISION trial (46%). The lower dose was well tolerated with a low incidence of pleural effusions (6%). The NiloRED study enrolled patients who were on nilotinib and had achieved MMR. With a median follow-up of 24 months after nilotinib dose reduction, 65 of 67 patients did not lose MMR. The 2 patients who lost MMR, regained it with any dose adjustments. This phenomena of transient rise in BCR-ABL1 after dose reduction was described in the BCR-ABL1 transcript levels modeling after a 50% dose reduction in patients who are in stable MMR.

Additional treatment strategies

Omacetaxine

Omacetaxine, a protein translation inhibitor formerly known as homoharringtonine, was approved by the FDA in 2012 for patients with CP or AP CML and with resistance or intolerance to at least two TKIs. This approval was based on a trial with MCyR rates of 20% in CP CML and MHR of 27% in AP CML. The final analysis, with 24 months follow-up, reported an MCyR and median OS of 18% and 40.3 months, respectively, in those with CP CML; 14% of patients with AP CML achieved MHR, for a median of 4.7 months. The most common toxicities were hematological, with at least grade 3 adverse events in 79% and 73% of CP and AP CML patients, respectively.

Asciminib (ABL001)

Asciminib is a targeted ABL inhibitor that binds to the myristoyl pocket of BCR-ABL1 instead of the catalytic pocket and induces the formation of an inactive kinase conformation. In the phase 1 trial, asciminib appeared to be well tolerated and resulted in durable activity in heavily pretreated CML patients, including CCyR and MMR. Mutations in the myristoyl pocket were rare but detectable in patients with relapse. Based on this activity, a randomized phase 3 trial was conducted for patients with CML-CP previously treated with ≥2 TKIs. Patients were randomized to asciminib 40 mg twice daily or bosutinib 500 mg once daily. At 24 weeks, the rate of MMR (25.5% versus 13.2%), MR4 (10.8% versus 5.3%) and MR4.5 (8.9% versus 1.3%) were higher with asciminib compared to bosutinib.

Other targeted approaches

A number of other treatment strategies for CML are under evaluation. These include approaches to eradicate CML stem cells using combination approaches with TKI and other agents such as JAK2 inhibitors (ruxolitinib), PD-1 blockade or PPAR-γ activators. Recent in vitro and in vivo work suggests that the combination of MDM2 and BET inhibitors may be used to upregulate p53-induced apoptosis and downregulate MYC to eradicate CML leukemia stem cells.

Stem cell transplantation

With the development of TKIs, rates of allogeneic SCT have dramatically declined for CP CML patients. Currently, allogeneic SCT is typically reserved for those who fail available TKIs and those with advanced-phase disease. For CP CML patients, typing can be considered at the time of failure or intolerance of second-line therapy when initiating third-line therapy. However, there may be scenarios when SCT may be considered at an earlier time. These may include, for example, pediatric or young adult patients who are adherent to therapy and fail first-line therapy with a second-generation TKI and do not have mutations associated with resistance that are amenable to treatment with an alternative TKI, or patients with T315I mutations. For patients with de novo AP (who have not received TKI therapy), treatment with a second-generation TKI is indicated as previously mentioned. SCT would be reserved for patients who are not responding appropriately to TKI therapy. The phase of disease has a significant impact on transplant outcome, as is highlighted by recent data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Outcomes are best in CP and are poor in BP, and consequently, timing of SCT before disease progression is critical. Data from CIBMTR are available for 2015 HLA-matched sibling donor transplants spanning 2005 to 2015. Three-year probability of survival for CP (N = 1611) was 66% ± 1%, for AP (N = 249) was 51% ± 4%, and for BP (N = 155) was 29% ± 4%. For CP patients, prior use of TKIs does not appear to influence transplant outcomes. For BP patients, inducing second CP yields outcomes comparable to AP transplant outcomes (ie, 20%-40% long-term, disease-free survival). Second CP can be induced by TKI therapy or by TKI therapy in combination with induction

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

chemotherapy similar to that used for acute leukemia. For children and young adults, a retrospective study of 449 patients found 5-year OS and leukemia-free survival after SCT of 76% and 57% in those aged <18 years and 74% and 60% in the 18- to 29-year-old group, respectively. In multivariate analysis, age and pre-SCT TKI use did not impact outcomes and older age was associated with an increased incidence of chronic graft-versus-host disease (cGVHD).

Across all ages, the incidence of acute GVHD ranges from 8% to 63%, with severe and fatal GVHD affecting up to 20% and 13% of patients, respectively. The use of alternative donors is expanding access to those in need of transplantation without a matched donor. Given the age of most CML patients and the fact that CML cells are highly susceptible to the graft-versus-leukemia (GVL) effect of an allograft, the use of reduced-intensity conditioning (RIC) regimens is common and has resulted in improved outcomes. The overall leukemia relapse rate after matched-unrelated donor SCT is somewhat lower than after matched-related transplantations, suggesting that minor antigen disparity enhances a GVL effect. In addition, relapse rates are higher after transplantation with T cell–depleted stem cells compared with unmanipulated stem cells, implicating that donor graft immune function is important in clearing residual disease. In a recent study of 306 CML patients predominantly treated with imatinib before SCT and receiving peripheral blood grafts and RIC, outcomes were examined for patients aged 40 to 49 years, 50 to 59 years, and 60 years or older. Disease stage at time of transplant was chronic, accelerated, and blast phase in 52%, 41%, and 7%, respectively. Unrelated donor RIC SCT was more common in older patients. Three-year OS was 54%, 52%, and 41%, respectively, and 3-year disease-free survival was 35%, 32%, and 16%, respectively. Three-year rates of chronic GVHD were 58%, 51%, and 43%, respectively, and 1-year treatment-related mortality was similar across age groups and was 18%, 20%, and 13%, respectively.

The potency of the GVL effect is further illustrated by the success of donor lymphocyte infusion (DLI) for relapsed disease after SCT. CML is the disease that responds best to DLI, although it is more effective in the treatment of CP relapse as compared to advanced-phase relapse. DLI induces remission in 54% to 93% of patients with early hematologic or cytogenetic relapse after allografting. TKI therapy is often effective in the setting of posttransplant relapse and can be used when GVHD is present and DLI is not an option. A review of 12 CP CML cases receiving imatinib after relapse reported that all patients achieved CCyR, and all but one had undetectable *BCR-ABL1* transcripts after 3 to 27 months of therapy (median, 9 months). Outcomes for patients with advanced-phase disease at relapse are not as good. A recent study of 14 advanced-phase patients reported CCyR rates of 71% and undetectable *BCR-ABL1* transcripts in 57%, either with imatinib or dasatinib treatment alone or in combination with donor lymphocyte infusion. The achievement of undetectable transcripts was very strongly associated with OS. Accordingly, molecular monitoring in the posttransplant setting is important to identify those at higher risk for relapse. Lastly, given the higher risk for relapse for advanced-phase patients after SCT, TKI therapy is often recommended for at least 1 year after SCT in these patients.

Parenting children

A small, but important, proportion of female patients are diagnosed with CML during the early stages of pregnancy as a result of routine laboratory tests. This difficult scenario must be handled sensitively. If presentation is in CP, there is no medical reason to terminate the pregnancy. However, TKIs are contraindicated in pregnancy because of an increased risk of congenital malformations, in particular omphalocele, and should not be used, particularly in the first and second trimesters. If the total white blood cell count is relatively low, some patients may complete the pregnancy without treatments. Others might be suitable for management by leukapheresis and/or interferon. For the woman presenting with advanced-phase disease, the balance of risk for mother and child should be frankly discussed with the patient and partner.

The more frequent situation is the patient who wishes to parent a child after the diagnosis is established. For male patients treated with imatinib, dasatinib, bosutinib or nilotinib there is a body of data to suggest that there is no increased risk to the mother during the pregnancy or to the infant.

For women on TKIs, treatment should be discontinued before conception. Ideally, the criteria for stopping TKI should be identical to that of trials for TFR, as approximately one-half the women are able to discontinue indefinitely. The remainder experience molecular recurrence within the first 6 months, but if they have conceived within that period, there is a high probability that they will reach the end of the pregnancy before they require treatment. In "real life," many women have not had prolonged deep responses at the time of considering motherhood. These situations should be handed individually, but possibilities include consideration of assisted conception techniques to minimize the time off treatment.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

If treatment is required during the pregnancy, then leukapheresis and interferon can be used early in the pregnancy. Because the teratogenic effect of imatinib appears to be during organogenesis, it is possible that it is safe in later pregnancy. However, a report of hydrops fetalis in a patient who received dasatinib in the second trimester underlines the need for caution. An important question, in particular for children, adolescents, and young adults on TKI therapy, is whether long-term TKI use impacts fertility. Case reports of primary ovarian insufficiency and oligospermia have been published, but, to date, very few data exist to inform decision making. These observations highlight the need for larger studies in younger patients examining TKI cessation, dose reduction, and/or intermittent TKI use.

KEY POINTS

- CML is a pluripotent hematopoietic stem cell neoplasm characterized by the *BCR-ABL1* fusion gene, which is derived from a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11), also known as the Ph chromosome.
- Typical blood findings include a left-shifted leukocytosis, with basophilia and often thrombocytosis.
- Prognosis has been remarkably improved by the development of TKIs and is dependent on the phase at presentation (CP, AP, or BP) and depth of response to therapy.
- There are now five TKIs available for use in CP CML. Imatinib, dasatinib, nilotinib, and bosutinib are frontline options for CP CML. Dasatinib, nilotinib, bosutinib, and ponatinib can be used in those with intolerance or resistance to prior TKI therapy.
- Meeting treatment milestones strongly influences prognosis and identifies those with resistance or loss of response, who require a switch to another TKI. Consensus guidelines are available to direct appropriate assessments during months 3, 6, and 12 and beyond and aid in management decisions.
- TKI cessation and TKI dose reductions are possible in some patients. However, patients must be carefully selected and closely monitored.

Bibliography

Abraham SA, Hopcroft LEM, Carrick E, et al. Dual targeting of p53 and c-Myc selectively eliminates leukaemic stem cells. *Nature*. 2016;534(7607):341-346.

Apperley JF. Part I: mechanisms of resistance to imatinib in chronic myeloid leukaemia. *Lancet Oncol*. 2007;8(11):1018-1029.

Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START-A trial. *J Clin Oncol*. 2009;27(21):3472-3479.

Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia, clinical lymphoma myeloma and leukemia, *Clin Lymphoma Myeloma Leuk*. 2017;17(12):897-901.

Atallah E, Patwardhan P, Mojebi A, et al. Systematic literature review of the efficacy of available interventions for patients with chronic-phase chronic myeloid leukemia (CML) who have previously been treated with ≥2 lines of tyrosine kinase inhibitors (TKIs). *Clin Lymphoma Myeloma Leuk*. 2020;20(suppl 1):S238-S239.

Atallah E, Schiffer CA, Radich JP et al. Assessment of outcomes after stopping tyrosine kinase inhibitors among patients with chronic myeloid leukemia: a nonrandomized clinical trial. *JAMA Oncol*. 2021;7(1):42-50.

Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.

Baccarani M, Druker BJ, Branford S, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. *Int J Hematol*. 2014;99(5):616-624.

Baccarani M, Rosti G, Castagnetti F, et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet Study. *Blood*. 2009;113(19):4497-4504.

Barber MC, Mauro MJ, Moslehi J. Cardiovascular care of patients with chronic myeloid leukemia (CML) on tyrosine kinase inhibitor (TKI) therapy. *Hematology (Am Soc Hematol Educ Program)*. 2017;2017:110-114.

Bhatia R. Novel approaches to therapy in CML. *Hematology (Am Soc Hematol Educ Program)*. 2017;2017:115-120.

Bonifazi F, de Vivo A, Rosti G. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood*. 2001;98(10):3074-3081.

Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TML. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016;34(24):2851-2857.

Branford S, Fletcher L, Cross NCP, et al. Desirable performance characteristics for bcr-abl measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. *Blood*. 2008;112(8):3330-3338.

Branford S, Rudzki Z, Parkinson I. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have bcr-abl kinase domain mutations. *Blood*. 2004;104(9):2926-2932.

Breccia M, Loglisci G, Salaroli A, Serrao A, Alimena G. Nilotinib-mediated increase in fasting glucose level is reversible, does not convert to type 2 diabetes and is likely correlated with increased body mass index. *Leuk Res*. 2012;36(4):e66-e67.

Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

leukaemia: results from the 24-month follow-up of the BELA trial. *Br J Haematol*. 2015;168(1):69-81.

Brümmendorf TH, Cortes JE, Khoury HJ, et al. Factors influencing long-term efficacy and tolerability of bosutinib in chronic phase chronic myeloid leukaemia resistant or intolerant to imatinib. *Br J Haematol*. 2016;172(1):97-110.

Castagnetti F, Gugliotta G, Breccia M, et al. The BCR-ABL1 transcript type influences response and outcome in Philadelphia chromosome-positive chronic myeloid leukemia patients treated frontline with imatinib. *Am J Hematol*. 2017;92(8):797-805.

Castagnetti F, Testoni N, Luatti S, et al. Deletions of the derivative chromosome 9 do not influence the response and the outcome of chronic myeloid leukemia in early chronic phase treated with imatinib mesylate: GIMEMA CML working party analysis. *J Clin Oncol*. 2010;28(16):2748-2754.

Chaudhury S, Sparapani R, Hu Z, et al. Outcomes of allogeneic hematopoietic cell transplantation in children and young adults with chronic myeloid leukemia: a CIBMTR cohort analysis. *Biol Blood Marrow Transplant*. 2016;22(6):1056-1064.

Chereda B, Melo JV. Natural course and biology of CML. *Ann Hematol*. 2015;94(suppl 2):107-121.

Christopoulos C, Dimakopoulou V, Rotas E. Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med*. 2008;358(10):1079-1080.

Cortes JE, Apperley J, Lomaia, E, et al. OPTIC primary analysis: a dose-optimization study of 3 starting doses of ponatinib (PON). *J Clin Oncol*. 2021;39(suppl 15):7000.

Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. *Lancet Haematol*. 2017;4(7):e310-e316.

Copland M, Hamilton A, Elrick LJ. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. *Blood*. 2006;107(11):4532-4539.

Cortes JE, Abruzzese E, Chelysheva E, Guha M, Wallis N, Apperley JF. The impact of dasatinib on pregnancy outcomes. *Am J Hematol*. 2015;90(12):1111-1115.

Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. *J Clin Oncol*. 2010;28(3):424-430.

Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. *J Clin Oncol*. 2018;36(3):231-237.

Cortes JE, Gambacorti-Passerini C, Deininger M, et al. Pregnancy outcomes in patients treated with bosutinib. *Int J Hematol Oncol*. 2020;9(2):IJH26.

Cortes JE, Jimenez CA, Mauro MJ, Geyer A, Pinilla-Ibarz J, Smith BD. Pleural effusion in dasatinib-treated patients with chronic myeloid leukemia in chronic phase: identification and management. *Clin Lymphoma Myeloma Leuk*. 2017;17(2):78-82.

Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367(22):2075-2088.

Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of Bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011;118(17):4567-4576.

Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: results with 24 months of follow-up. *Cancer*. 2015;121(10):1637-1644.

Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term Bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. *Am J Hematol*. 2016; 91(12):1206-1214.

Cortes JE, Lomaia E, Turkina A, et al. Interim analysis (IA) of OPTIC: a dose-ranging study of three ponatinib (PON) starting doses. *J Clin Oncol*. 2020;38(suppl 15):7502.

Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol*. 2016;34(20):2333-2340.

Deininger MW, Hodgson JG, Shah NP, et al. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. *Blood*. 2016;127(6):703-712.

Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of interferon vs STI571 (IRIS) 8-year follow-up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. *Blood*. 2009;114(22):1126.

Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the bcr-abl TK in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001;344(14):1038-1042.

Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the bcr-abl tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344(14):1031-1037.

Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res*. 2011;35(5):626-630.

Etienne G, Guilhot J, Rea D, et al. Long-term follow-up of the French Stop imatinib (STIM1) Study in patients with chronic myeloid leukemia. *J Clin Oncol*. 2017;35(3):298-305.

Fabarius A, Leitner A, Hochhaus A, et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML study IV. *Blood*. 2011;118(26):6760-6768.

Fassoni AC, Baldow C, Roeder I, Glauche I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. *Haematologica*. 2018;103(11):1825-1834.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst*. 2011;103(7):553-561.

Gambacorti-Passerini C, Cortes JE, Kantarjian HM et al. Safety and efficacy of second-line Bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase 1/2 study. *Haematologica*. 2018;103(8):1298-1307.

Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *Am J Hematol*. 2015;90(9):755-768.

Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. *Blood*. 2009;114:4361-4368.

Giles FJ, Abruzzese E, Rosti G, et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. *Leukemia*. 2010;24:1299-1301.

Guilhot F, Chastang C, Michallet M, et al; French Chronic Myeloid Leukemia Study Group. Interferon-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *N Engl J Med*. 1997;337(4):223-229.

Hadzijusufovic E, Albrecht-Schgoer K, Huber K, et al. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia*. 2017;31(11):2388-2397.

Hanfstein B, Lauseker M, Hehlmann R, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. *Haematologica*. 2014;99(9):1441-1447.

Hanfstein B, Müller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia*. 2012;26(9):2096-2102.

Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med*. 1998;338(14):962-968.

Hehlmann R. How I treat CML blast crisis. *Blood*. 2012; 120(4):737-747.

Hehlmann R, Hanfstein B, Muller MC, et al. The prognostic significance of early molecular and cytogenetic response for long-term progression-free and overall survival in imatinib-treated chronic myeloid leukemia. *J Clin Oncol*. 2012;30(15):6510.

Hehlmann R, Lauseker M, Saußele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31(11):2398-2406.

Hehlmann R, Müller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *J Clin Oncol*. 2014;32(5):415-423.

Hehlmann R, Saußele S, Voskanyan A, Silver RT. Management of CML-blast crisis. *Best Pract Res Clin Haematol*. 2016;29(3):295-307.

Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood*. 2016;127(4):392-399.

Hobemicht SL, Schweiger B, Zeitler P, Wang M, Hunger SP. Acquired growth hormone deficiency in a girl with chronic myelogenous leukemia treated with tyrosine kinase inhibitor therapy. *Pediatr Blood Cancer*. 2011;56(4):671-673.

Hochhaus A, Baccarani M, Silver R, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34:966-984.

Hochhaus A, Boquimpani C, Rea D. Efficacy and safety results from ASCEMBL, a multicenter, open-label, phase 3 study of asciminib, a first-in-class STAMP inhibitor, vs bosutinib (BOS) in patients (Pts) with chronic myeloid leukemia in chronic phase (CML-CP) previously treated with ≥2 tyrosine kinase inhibitors (TKIs) [abstract]. *Blood*. 2020;136(suppl 2):LBA-4.

Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood*. 2007;109(6):2303-2309.

Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376(10):917-927.

Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;31(7):1525-1531.

Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044-1054.

Hochhaus A, Saglio G, Larson RA, et al. Nilotinib is associated with a reduced incidence of bcr-abl mutations vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Blood*. 2013;121(18):3703-3708.

Hoffmann VS, Baccarani M, Lindoerfer D, et al. The EUTOS prognostic score: review and validation in 1288 patients with CML treated frontline with imatinib. *Leukemia*. 2013; 27(10):2016-2022.

Howlader N, Noone AM, Krapcho M, et al, eds. SEER cancer statistics review. Available at: https://seer.cancer.gov/csr/1975_2014/. Accessed 22 April 2022.

Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003;349(15):1423-1432.

Hughes TP, Lipton JH, Spector N, et al. Deep molecular responses achieved in patients with CML-CP who are switched to nilotinib after long-term imatinib. *Blood*. 2014;124(5):729-736.

Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019;381(24):2315-2326.

Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavrillaki on 10 December 2022

chronic phase treated with frontline nilotinib or imatinib. *Blood*. 2014;123(9):1353-1360.

Hughes TP, Yeow-Tee G, Ottman OG, et al. Expanded phase 1 study of ABL001, a potent, allosteric inhibitor of bcr-abl, reveals significant and durable responses in patients with CML-chronic phase with failure of prior TKI therapy. *Blood*. 2016;128:625.

Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood*. 2011;117(14):3733-3736.

Jain N, Cortes J, Ravandi F, et al. Inotuzumab ozogamicin in combination with bosutinib for patients with relapsed or refractory Ph+ ALL or CML in lymphoid blast phase [abstract]. *Blood*. 2017;130(suppl 1):143.

Jain P, Kantarjian HM, Ghorab A, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blastphase in the tyrosine kinase inhibitor era: cohort study of 477 patients. *Cancer*. 2017;123(22):4391-4402.

Jørgensen HG, Allan EK, Jordanides NE, Mountford JC, Holyoake TL. Nilotinib exerts equipotent antiproliferative effects to imatinib and does not induce apoptosis in CD34+ CML cells. *Blood*. 2007;109(9):4016-4019.

Kantarjian HM, Cortes J, O'Brien S. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. *Blood*. 2002;99(10):3547-3553.

Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis [published correction appears in *Leukemia*. 2021;35(7):2142-2143]. *Leukemia*. 2021;35(2):440-453.

Kantarjian HM, Pasquini R, Lévy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. *Cancer*. 2009;115(18):4136-4147.

Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med*. 2002;346(9):645-652.

Kantarjian H, Talpaz M, O'Brien S. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. *Blood*. 2004; 103(8): 2873-2878.

Kantarjian H, Talpaz M, O'Brien S, et al. Survival benefit with imatinib mesylate therapy in patients with accelerated-phase chronic myelogenous leukemia—comparison with historic experience. *Cancer*. 2005;103(10):2099-2108.

Kebriaei P, Detry MA, Giralt S, et al. Long-term follow-up of allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning for patients with chronic myeloid leukemia. *Blood*. 2007;110(9):3456-3462.

Khorashad JS, Kelley TW, Szankasi P, et al. BCR-ABL1 compound mutations in tyrosine kinase inhibitor-resistant CML: frequency and clonal relationships. *Blood*. 2013;121(3):489-498.

le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*. 2012;26(6):1189-1194.

Lipton JH, Bryden P, Sidhu MK, et al. Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors. *Leuk Res*. 2015;39(1):58-64.

Lipton JH, Chuah C, Guerci-Bresler A, et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(5):612-621.

Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop imatinib (STIM) trial. *Lancet Oncol*. 2010;11(11):1029-1035.

Marzocchi G, Castagnetti F, Luatti S, et al. Variant philadelphia translocations: molecular-cytogenetic characterization and prognostic influence on frontline imatinib therapy, a GIMEMA working party on CML analysis. *Blood*. 2011;117(25):6793-6800.

Mauro MJ, Baccarani M, Cervantes F, et al. Dasatinib 2-year efficacy in patients with chronic-phase chronic myelogenous leukemia (CML-CP) with resistance or intolerance to imatinib (START-C) [abstract]. *J Clin Oncol*. 2008;26(suppl 15). Abstract 7009.

McGlave PB, Shu XO, Wen W, et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. *Blood*. 2000;95(7):2219-2225.

Melo JV, Gordon DE, Cross NC, Goldman JM. The ABL-BCR fusion gene is expressed in chronic myeloid leukemia. *Blood*. 1993;81(1):158-165.

Millot F, Guilhot J, Baruchel A, et al. Growth deceleration in children treated with imatinib for chronic myeloid leukaemia. *Eur J Cancer*. 2014;50(18):3206-3211.

Moslehi JJ, Deininger M. Tyrosine kinase inhibitor–associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol*. 2015;33(35):4210-4218.

Müller MC, Cervantes F, Hjorth-Hansen H, et al. Ponatinib in chronic myeloid leukemia (CML): consensus on patient treatment and management from a European expert panel. *Crit Rev Oncol Hematol*. 2017;120:52-59.

Müller MC, Cortes JE, Kim DW, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting bcr-abl mutations. *Blood*. 2009;114(24):4944-4953.

Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2020;126(1):67-75.

Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009;113(22):5401-5411.

Ohanian M, Kantarjian HM, Quintas-Cardama A, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clin Lymphoma Myeloma Leuk*. 2014;14(2):155-162.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Olavarria E, Ottmann OG, Deininger M, et al. Chronic Leukemia Working Party of the European Group of Bone and Marrow Transplantation (EBMT). Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Leukemia*. 2003;17(9):1707-1712.

Olavarria E, Siddique S, Griffiths MJ, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. *Blood*. 2007;110(13):4614-4617.

Palandri F, Amabile M, Rosti G, et al. Imatinib therapy for chronic myeloid leukemia patients who relapse after allogeneic stem cell transplantation: a molecular analysis. *Bone Marrow Transplant*. 2007;39(3):189-191.

Pfirrmann M, Evtimova D, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *J Cancer Res Clin Oncol*. 2017;143(5):843-850.

Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. *Blood*. 2008;111(12):5505-5508.

Qiang W, Antelope O, Zabriskie MS, et al. Mechanisms of resistance to the BCR-ABL1 allosteric inhibitor asciminib. *Leukemia*. 2017;31(12):2844-2847.

Quintás-Cardama A, Kantarjian H, Shan J, et al. Prognostic impact of deletions of derivative chromosome 9 in patients with chronic myelogenous leukemia treated with nilotinib or dasatinib. *Cancer*. 2011;117(22):5085-5093.

Radich JP, Gooley T, Bryant E. The significance of BCRABL molecular detection in chronic myeloid leukemia patients "late," 18 months or more after transplantation. *Blood*. 2001;98(6):1701-1707.

Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. *Blood*. 2012;120(19):3898-3905.

Rea D, Etienne G, Nicolini F, et al. First-line imatinib mesylate in patients with newly diagnosed accelerated phase-chronic myeloid leukemia. *Leukemia*. 2012;26(10):2254-2259.

Rea D, Mirault T, Cluzeau T, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. *Haematologica*. 2014;99(7):1197-1203.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed April 22, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Richter J, Söderlund S, Lübking A, et al. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? *J Clin Oncol*. 2014;32(25):2821-2823.

Ries LAG, Smith M, Gurney JG, et al, eds. Cancer incidence and survival among children and adolescents: United States SEER program, 1975-1995. National Institutes of Health Publication 99-4649. National Cancer Institute, SEER Program; 1999:46-49.

Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;122(4):515-522.

Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;32(5):424-430.

Ruggiu M, Oberkampf F, Ghez D, et al. Azacytidine in combination with tyrosine kinase inhibitors induced durable responses in patients with advanced phase chronic myelogenous leukemia. *Leuk Lymphoma*. 2018;59(7):1659-1665.

Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-757.

Sawyers CL. Signal transduction pathways involved in BCR-ABL transformation. *Baillieres Clin Haematol*. 1997;10(2):223-231.

Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med*. 2004;351(20):2134-2135.

Shah NP, Guilhot F, Cortes JE, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. *Blood*. 2014; 123(15):2317-2324.

Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2008;26(19):3204-3212.

Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. *Am J Hematol*. 2016; 91(9):869-874.

Shah NP, Wallis N, Farber HW, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. *Am J Hematol*. 2015;90(11):1060-1064.

Soverini S, De Benedittis C, Castagnetti F, et al. In chronic myeloid leukemia patients on second-line tyrosine kinase inhibitor therapy, deep sequencing of BCR-ABL1 at the time of warning may allow sensitive detection of emerging drug-resistant mutants. *BMC Cancer*. 2016;16(1):572-577.

Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*. 2016;30(8):1648-1671.

Szakács Z, Hegyi PJ, Farkas N, et al. Pregnancy outcomes of women whom spouse fathered children after tyrosine kinase inhibitor therapy for chronic myeloid leukemia: a systematic review. *PLoS One*. 2020;15(12):e0243045.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022

Valent P, Hadzijusufovic E, Schernthaner GH, Wolf D, Rea D, le Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood*. 2015;125(6):901-906.

Wang W, Cortes JE, Lin P, et al. Impact of trisomy 8 on treatment response and survival of patients with chronic myelogenous leukemia in the era of tyrosine kinase inhibitors. *Leukemia*. 2015;29(11):2263-2266.

Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. *Blood*. 2016;127(22):2742-2750.

Warlick E, Ahn KW, Pedersen TL, et al. Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic myelogenous leukemia patients undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. *Blood*. 2012;119(17):4083-4090.

Wright MP, Shepherd JD, Barnett MJ, et al. Response to tyrosine kinase inhibitor therapy in patients with chronic myelogenous leukemia relapsing in chronic and advanced phase following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2010;16(5):639-646.

Wylie AA, Schoepfer J, Jahnke W, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. *Nature*. 2017;543(7647):733-737.

Yeung DT, Osborn MP, White DL, et al. TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. *Blood*. 2015; 125(6):915-923.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908690/chapter_16.pdf by Eleni Gavriilaki on 10 December 2022